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PRELIMINARY INVESTIGATION OF EFFECTS ON THE ENVIRONMENT OF BORON, INDIUM NICKEL, SELENIUM, TIN, VANADIUM AND THEIR COMPOUNDS

VOLUME II - INDIUM

VERSAR, INCORPORATED

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY

AUGUST 1975

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PRELIMINARY INVESTIGATION OF EFFECTS ON THE ENVIRONMENT OF BORON, INDIUM NICKEL, SELENIUM, TIN, VANADIUM AND THEIR COMPOUNDS

VOLUME II

INDIUM

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PRELIMINARY INVESTIGATION OF EFFECTS ON THE ENVIRONMENT OF BORON, INDIUM NICKEL, SELENIUM, TIN, VANADIUM AND THEIR COMPOUNDS

Volume II

Indium

Contract No. 68-01-2215

Project Officer

Farley Fisher

Prepared for

Office of Toxic Substances
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Volume II

Preliminary Investigation of Effects
on Environment of Indium and Its Compounds

FOREWORD

This is Volume II of a series of six reports on the environmental effects of boron, indium, nickel, selenium, tin, and vanadium and their compounds. The information is based on literature reviews, direct contact with representatives of companies involved in the production or use of the materials, and consultation with knowledgeable individuals from industry, academic institutions and the Federal Government.

I. INDIUM INDUSTRY IN THE UNITED STATES

A. Producers and Sites

Table I lists commercially significant chemical products and the companies involved. For this study significant is defined as production exceeding approximately $1,000 value. Other materials may also be included in the discussion because of their unusual properties, such as toxicity, or their anticipated future significance.

Table 1[1]

Indium Products and Producers

Chemical	Producer: Company, subordination	Producer: Location
Indium (metal)	American Smelting and Refining Co.	[illegible]nver, Colo.
	Atomergic Chemetals Co. Gallard-Schesinger	Carle Place, N.Y.
	Electronic Space Products, Inc.	Los Angeles, Calif.
	Fairmount Chemical Co., Inc.	Newark, N.J.
	Goldsmith, D. F. Chem. & Metal Corp.	Evanston, Ill.
	Indium Corp. of America	Utica, N.Y.
	Kawecki Berylco Ind., Inc.	New York, N.Y.
	Rocky Mountain Research, Inc.	Golden, Col.
	United Mineral & Chem. Corp.	New York, N.Y.
	Var-Lac-Oid Chem. Co.	Elizabeth, N.J.
Indium acetylacetonate	MacKenzie Chem. Works, Inc.	Central Islip, N.Y.
Indium antimonide	Monsanto Co. Monsanto Commercial Products Co. Electronic Products	St. Peters, Mo.
Indium arsenide	Monsanto Co. Monsanto Commercial Products Co. Electronic Products	St. Peters, Mo.
Indium carbonate	City Chem. Corp.	Jersey City, N.J.
Indium cyanide	The Indium Corp. of America	Utica, N.Y.

Table 1 (Con't)

Indium Products and Producers

Chemical	Producer: Company, subordination	Location
Indium fluoborate	Allied Chem. Corp. Specialty Chems. Div.	Marcus Hook, Pa.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	The Indium Corp. of America	Utica, N.Y.
Indium hydroxide	American Smelting and Refining Co.	Denver, Colo.
	The Indium Corp. of America	Utica, N.Y.
Indium iodide, anhydrous	Ventron Corp. Alfa Products Div.	Beverly, Mass.
Indium nitrate	The Indium Corp. of America	Utica, N.Y.
Indium oxide (Indium sesquioxide) (Indium trioxide)	American Smelting and Refining Co.	Denver, Colo.
	Apache Chems., Inc.	Rockford, Ill.
	Fairmount Chem. Co., Inc.	Newark, N.J.
	The Indium Corp. of America	Utica, N.Y.
Indium phosphide	Apache Chems., Inc.	Rockford, Ill.
Indium sulfamate	The Indium Corp. of America	Utica, N.Y.
Indium sulfate	Fairmount Chem. Co., Inc.	Newark, N.Y.
	The Indium Corp. of America	Utica, N.Y.
Indium sulfide	The Indium Corp. of America	Utica, N.Y.
Indium tribromide	The Indium Corp. of America	Utica, N.Y.
Indium trichloride (Indium chloride)	American Smelting and Refining Co.	Denver, Colo.
	Fairmount Chem. Co., Inc.	Newark, N.J.
	The Indium Corp. of America	Utica, N.Y.
	Ventron Corp. Alfa Products Div.	Beverly, Mass.

Table 1 (Con't)
Indium Products and Producers

Chemical	Producer: Company, subordination	Producer: Location
Indium trifluoride	The Indium Corp. of America	Utica, N.Y.
	Ozark-Mahoning Co.	Tulsa, Okla.
Indium triiodide	The Indium Corp. of America	Utica, N.Y.

B. Costs

The price of indium has declined steadily since 1940, when it first became available commercially in the United States. The first quoted price in September, 1930 was $15.00 per gram. This dropped to $0.072 per gram by December, 1945, as demand developed and supplies became available. Since then the price has fluctuated within a relatively narrow range and stabilized at $0.056 per gram in September, 1968. Imported material was available at substantial discounts from 1971 through 1972, as low as $0.030 to 0.032 per gram. Prices are now back to normal.(2) The producer prices of indium during 1972 were unchanged at $0.080 per gram for sticks in lots of less than 3.1 kg; 3.1 kg ingots were $0.066 per gram and lots of 320 sticks were priced at $0.056 per gram.(3)

The price of indium cannot be discussed without considering the association of indium with zinc since their resources and production are interrelated. As a consequence of this association, the output of indium does not readily respond to indium price advances. The amount of reserves of indium at recovery facilities is another factor to be considered.(4)

C. Physical Properties of Important Commercial Indium Compounds

The three most important indium compounds are the metal, the oxide and the sulfate. Physical properties of these are presented in Table 2.

Table 2 (4,5)

Physical Properties

Chemical	Specific Gravity	Melting Point °C	Boiling Point °C	Solubility Water g/100cc °C	Comments
Indium	7.30^{20}	156.61	2000 ± 10	i (hot & cold)*	Malleable, ductile; Softer than lead
Indium sesquioxide	7.179 7.179		volat. 850	i cold	
Indium sulfate		3.438		s cold vs hot	

*Finely divided indium forms hydroxide on contact with water.

II. PRODUCTION

A. Domestic Production

Company	Location
American Smelting & Refining Company (ASARCO)	Denver, Colo.

The above firm was the only reported domestic producer of indium for 1972. They recovered indium from flue dusts and residues in which indium's source materials were concentrated during the processing of zinc ores and concentrates. Other firms sent them flue dusts and zinc processing residues for recovery of the indium. Production figures are not available. U.S. zinc smelter production of 15,000 grams of indium was reported for 1968 only after considering the number of years which had elapsed. The firm considers production figures proprietary information.

Despite the limited domestic extraction of indium, it is not a rare element. As late as 1924, indium was still a laboratory curiosity. Today indium is available in considerable quantities, in many sections of the world.(6)

ASARCO provides a commercial grade indium of 99.97 per cent purity and a refined product of unspecified purity. Indium of 99.9999 per cent purity is refined by the Indium Corporation of America.

Based on the meager knowledge of the indium content of zinc reserves, the domestic reserves of indium are estimated at 400,000 grams. The reserves of indium for the rest of the world are estimated at 2 million grams of recoverable indium.(4)

Indium is not on the list of strategic and critical materials and there are no Government programs for stockpiling or production assistance for indium. The demand for indium is fulfilled by domestic production and substantial imports.(4) U.S. producers maintain reserve supplies of recovered indium. Details of the amount stockpiled are not available.

B. Imports of Indium

The imports of indium metal in 1972 increased 62 per cent over 1971 imports.

The increase is attributed to the lower price. Dealers could trade foreign metal for more than 3 cents per gram less than the domestic producer price. The total 1972 imports were 20,200 grams with the suppliers as follows: Canada, 33%; U.S.S.R, 27%; Peru, 15%; United Kingdom, 14% and others 11%.[3]

C. Production Process

Indium recovery in the U.S. is a byproduct of primary zinc production. The details of the process used by ASARCO are not available. Two independent processes are known to have been developed by the company. In one, indium-containing residues are leached with strong acid and indium precipitated as a phosphate. This is then treated with hot sodium hydroxide to obtain indium hydroxide. The hydroxide is reduced to the metal and further refined electrolitically. In the other method, a chloride slag obtained from zinc-lead bullion is leached with dilute sulfuric acid and an indium-zinc sponge produced by the addition of zinc dust. The sponge is further purified by chlorination followed by electrolysis.[7]

III. USES

A. Indium Metal

Indium was first used commercially over 30 years ago as a dental alloy. The only available breakdown on the uses of indium is on an international, rather than domestic basis. (See Figure 1) This information was published in 1973.(2)

B. Uses of Indium and its Compounds

The solder and alloy industries offer the best opportunity for growth for the indium market. This is because indium increases hardness and fatigue resistance and improves corrosion resistance, producing generally high quality solders and braze-bonded connections.

The use of indium in semi-conductor devices is closely tied to silicon and germanium device production where indium is used to form the alloy junction. The use of germanium devices is declining. They are being replaced by silicon devices. The use of indium-containing solders in silicon device fabrication, therefore, is on the increase.

Substitutes are available for most uses of indium. Continuing research in the transistor field could lead to replacement of the germanium-indium type of transistor. Gallium can be used instead of indium in dental alloys and glass joint seals; however, gallium is more expensive than indium. Since the cost of materials is a relatively small part of the end product cost in most of the uses, adequacy of supply and desirable properties (or fewer undesirable properties) are more likely to determine which element is used.(4) A detailed summary of current indium usage is presented in Table 3.

C. Forecast and Future Use for Indium

The U.S. Bureau of Mines prepared a forecast of the requirements for indium by the year 2000. 1968 was used as the base year and the annual growth rate projected for total population was 1.6 per cent for 1968 to 2000. Projecting from an estimated consumption of 18,000 grams of indium in 1968, the

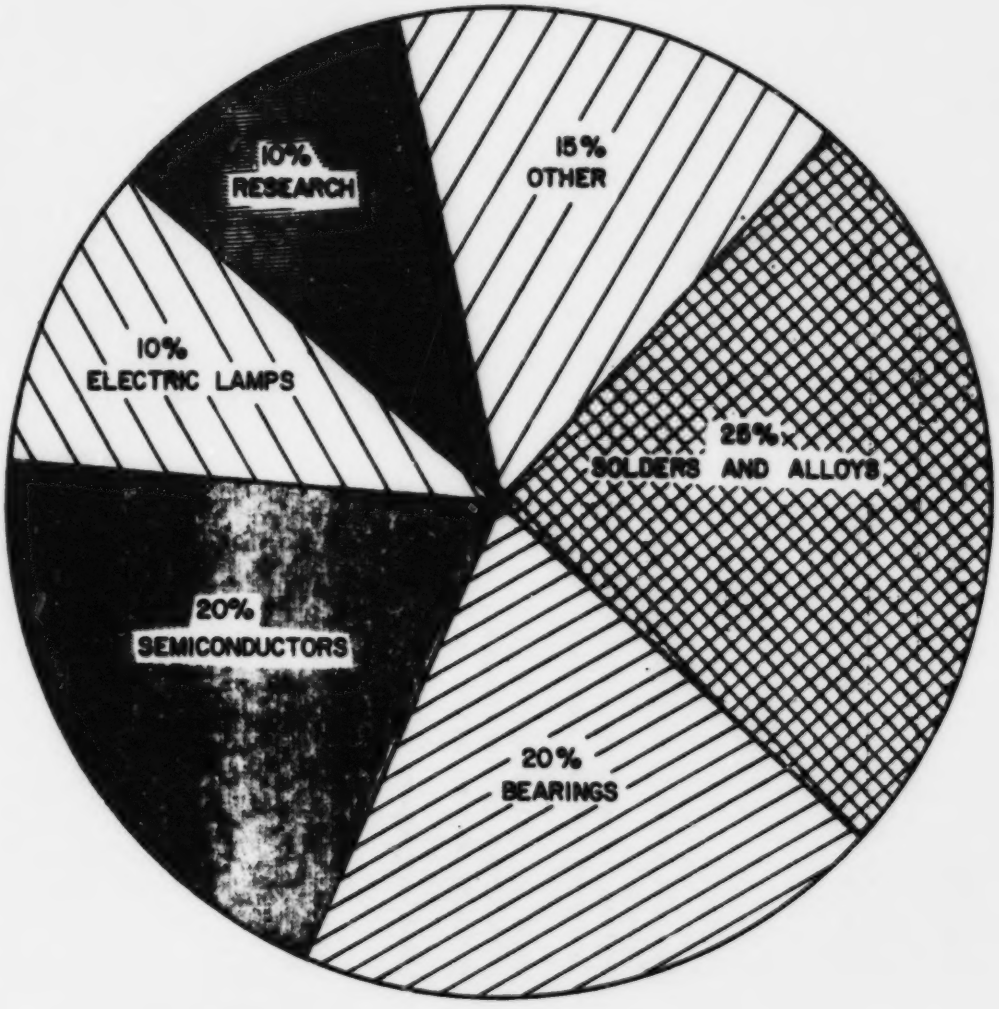

Figure I

International use of Indium

Table 3.
(2,8)
... of Indium

Compound	Use	Purpose	Comments
Indium	Dental alloy		
	Solder and alloy industries	Produces high quality solders and braze-bonded connectors	
	Automotive bearings		Strictly European use
	Low pressure sodium lamps		Strictly European use
	Other	Nuclear reactor control rod alloys Catalysts Indium oxide fuel cells Cryogenic gasket material	
Indium Oxide	Glass	Used for coloring. A light to dark brown can be obtained, depending on the amount used	
Indium Sulfate	Electroplating	Used to prepare sulfate electrolytes	
Radioisotopes of Indium & Indium Compounds	Medical	Treatment of cancer and diagnostic organ scanning	

demand in year 2000 will be in the range of 21,000 to 37,000 grams, or a median of 29,000. This estimate was postulated on normal technological development, growth in existing uses, and no new breakthroughs.(4)

A new use developed by Western Electric and now being implemented by the Bell System is indium-plated components. Splicing connectors which employ indium-plated contacts are used with both aluminum and copper cables. One type connector is for splicing, bridging and butt splicing. Special tools have been designed for installing the connectors. Coating of the contacts with indium may present a chance for indium to spill over into the environment. The Bell System will use about a billion of these units.(9) In terms of the quantity of indium involved, this could amount to as much as three per cent of the total consumed in the United States. A supply problem is not anticipated. One company supplies indium sulfate plating solution to a number of contractors. They provide the indium-plated components in a "sealed system".(9)

IV. CURRENT PRACTICES

Indium and most of its compounds are considered to be locally a moderately toxic irritant. Indium ingested or inhaled into the system is considered severely toxic.

Indium in the form of dust may pose a moderate fire hazard in the presence of heat or flame.[10] Heated indium burns with a nonluminous blue-red flame to form indium sesquioxide. Approved respiratory equipment should be worn when burning indium. Carbon dioxide, dry chemicals, or foam can be used to extinguish an indium or an indium sesquioxide fire.[11]

Indium metal requires careful packing in bars, stick, foil, or shot for shipment to prevent pieces from sticking and to avoid cutting or denting of the shapes. Indium wire, in continuous lengths of 0.081 cm. minimum diameter is available in 0.5, 2.5 or 10 kilogram spools.[12]

Indium sulfate is available as a dry powder or in solution and is packed in bottles in units of one gram. Indium sesquioxide is available as dry powder packed in bottles in 900 gram units.[12]

V. ENVIRONMENTAL CONTAMINATION

A. From Production

Fairly routine procedures are used to recover indium as a byproduct of primary zinc production. (See IIIB) Operational data are not available; however, indium contamination of the environment should not pose a problem. This is because special procedures are required to take care of wastes (lead for instance) and contaminants (such as sulfur dioxide) present or developed during the production of primary zinc.

B. From Use and Disposal

The environmental hazard from indium appears to result from the use and disposal of radioactive isotopes and not chemical toxicity. In a study in Cape Town, South Africa, for example, indium-113 was still detectable as a bolus with an average radioactivity on the order of 10^{-4} microcuries per ml, even after travelling a considerable distance after being dumped into the city sewage system by a hospital.(13)

The use of carrier-free radioactive isotopes of indium in medical applications essentially eliminates the hazard from chemical toxicity. The use of indium as a lubricant and the use of indium antimonide for semi-conductor purposes appear to pose no direct environmental threat.

Indium and its compounds are rated moderately toxic. Recovered indium has a recycled value so a minimum quantity is discarded. Closed containers are required for the disposal of indium and its compounds.(11) In view of the practices indicated above and the limited applications and small amounts involved, indium and its compounds do not seem to pose environmental contamination problems either in production or use.

C. Inadvertent Sources

Indium is recovered commercially as a byproduct in processing zinc-bearing ores. Over and above that obtained by design in the procedures for recovering zinc (as well as other nonferrous materials), there is some concentration of indium in the residuals. In this manner indium may get into

the environment from flue and Cottrell precipitator dusts, residues from zinc retorts, residues from cadmium recovery, lead blast furnace slags and crude zinc and lead. The amounts of indium involved in these inadvertent sources should not cause problems unless trace amounts of indium should prove harmful. Furthermore, should the supply of indium become tight, some of these could become valuable for recovery of indium.[4]

VI. ANALYSIS

A. Detection[7]

1. Physical techniques - Indium may be detected by the characteristic blue-violet color it imparts to a flame at 4511.31 and 4101.76 Å. As little as 0.01 to 0.02 ppm indium can be detected by this technique. Indium may also be detected spectroscopically by identification of the indium lines at the following wavelengths given in decreasing order of intensity: 4511.31, 4101.76, 3256.09, and 3039.36 Å.

2. Chemical Techniques - There are no specific chemical methods available for the detection of indium. Of the methods used, the Alizarin and Quinalizarin method is recommended as suitable and sensitive.

> *Alizarin and Quinalizarin Method.* Indium forms a dark red lake with alizarin, and a violet lake with quinalizarin in ammoniacal solution. The effect of aluminum can be masked by fluoride, and that of zinc, manganese, ferrous iron, cobalt, and nickel by cyanide. The limit of detection is 0.01 to 1 µg of indium, depending on the conditions used.[7]

B. Quantitative Analysis[7]

There are a number of classical analytical methods available for the determination of indium, involving gravimetric or titrimetric procedures. In the gravimetric methods indium is precipitated as the hydroxide, then ignited to the oxide In_2O_3. Prior to the precipitation of indium, indium must be separated from interfering elements. Two schemes are presented which, although tedious, are used to remove interfering elements.

Other gravimetric methods obtain the indium as the sulfide or hydroxyquinolinate instead of as the oxide. Non-gravimetric methods listed are electrodeposition and titrimetric methods. Unfortunately the quantitative methods of analysis are not characterized as to their sensitivity.

VII. CHEMICAL REACTIVITY

A. Environmental and Use Associated Reactions

Indium metal is unaffected by air at ordinary temperatures, but at red heat it burns with a blue flame to form the oxide, In_2O_3. The metal reacts with sulfur and the halides when heated.

VIII. BIOLOGY

A. Distribution and Transport

Different chemical compounds of the various radionuclides of indium are organ specific, hence radioactive indium compounds are used in diagnostic organ scanning.[14,15] The mode of administration of the indium compound also affects its biological behavior. Regardless of the mode of administration, the predominant accumulation of radioindium several hours after administration occurs within the organs of the reticuloendothelial system (RES): the liver, spleen, and bone marrow.[16] In pregnant rats, an initial placental retention of radioindium is followed by a gradual release of the indium.[16,17] Two times the indium found in the blood was found in the mammary glands of lactating rats, but very little was found in the milk. The indium does not cross to the fetus.[18] Subcutaneously injected radiocolloid indium-111 in dogs was primarily distributed in the injection site, the regional lymph nodes, and the liver, via the systemic veins.[19] The largest concentrations of radioindium after intravenous injection of white mice occurred in the liver and spleen, with little activity recovered from the blood, kidneys, or lungs.[19] In humans, the distribution of injected indium colloid made with gelatin and phosphate buffer appears to be 80 per cent in liver, 3 per cent in spleen, and 10 per cent in the red bone marrow.[20] Indium distribution was studied 2 to 48 hours after an oral dose of 0.5 microcuries of indium-114 in a basic solution. Maximum activity was noted in the kidneys, liver and spleen; minimum activity, in the heart and epididymis. After intratracheal administration, the lungs had the highest activity. Most of the excretion was via the feces.[21]

The distribution of injected radioindium can be controlled by controlling the pH of the preparation. The indium activity in the blood was high with a pH of 3.5 ± 1.0. With a pH of 10.5 ± 0.5, approximately 80 per cent of the indium was localized in the liver.[22]

Indium-113M, with a half-life of 100 minutes, can easily be generated from tin-113, and if it is carrier free, toxicity effects are reduced since less indium is utilized.[23] Intravenously injected ionic indium-113M becomes bound to the plasma protein, transferrin.[24] Transferrin was

saturated with a plasma indium concentration of four micrograms per ml. of normal plasma. Excess indium above this level was bound mainly to alpha-2-globulins.[24] Indium injected in this form or as indium transferrin[25] or indium human serum albumin[26] complexes is useful for blood volume studies, cardiac blood pool and placental scanning. Ninety-five per cent of indium-113M human serum albumin microaggregates, ranging in size from 10 to 150 microns, were retained in the lungs thirty minutes after an intravenous injection into experimental animals.[27] Indium is removed from the blood by the liver, spleen, and the kidneys. The kidney uptake of ionic indium injected into mice is the greatest of all organs on a per gram basis. The liver and spleen rapidly accumulate hydrated indium oxide.[28]

Colloidal indium-111 and indium-111 transferrin distribute evenly throughout the cerebrospinal fluid compartment.[29] Indium phosphate colloid, however, tends to accumulate in the basal cisterns and is, therefore, not useful for cerebrospinal scanning.[30] Indium phosphate colloids injected intravenously are accumulated by the reticuloendothelial system and are useful for liver, spleen and bone marrow scanning.[25]

Eighty per cent of the colloidal indium-113M injected intravenously with mannitol or gelatin is found in the liver. Without these additives, only 60 per cent of the indium appears in the liver, while 15 per cent is located in the lungs.[31] Eighty-five per cent of injected indium-113M hydroxide colloids was localized in the liver of humans.[32] Gallium hydroxide, which blocks the RES, decreased the liver uptake of indium hydroxide.[33] The liver uptake of colloidal indium-113M is greater than for gold-198;[34] however, the indium uptake is diminished in the liver in favor of the spleen if the liver function is impaired. This occurs in patients with polycythemia vera, osteomyelofibrosis, primary carcinoma of the liver, metastases in the liver and liver cirrhosis.[35]

Indium-113M chloride stabilized by gelatin becomes bound to the gamma-globulins after intravenous injection into man and animals. Five to ten minutes after injection, the heart, large abdominal vessels, and cerebral circulation become radiopaque.[36] Placental localization was correctly accomplished in 38 of 41 patients after intravenous injection of indium chloride.[37] Colloidal indium-113M chloride is accumulated by liver, spleen, and bone marrow.[38,39]

Indium-111 chloride is selectively accumulated by some types of malignant tumors.[40] The subcellular soluble fraction from epidermoid carcinoma in rats contained more indium radioactivity than the same fraction from the liver.[41]

Indium-iron hydroxide complex injected intravenously becomes localized in the lung.[25,36] Fifteen minutes after injection, 90 per cent of the radioactivity was found in the lung of the mouse. About 45 per cent of the dose remained in the lungs 42 days later. The highest activity observed in the liver, 13 per cent of the injected dose, occurred after two days. The peak activity in the carcass was 35 per cent after 14 days.[42] On the average, 83 per cent of injected indium-113M ferric hydroxide particles, 20 to 50 microns in size, were taken up by the lungs in rats.[43] Significant deposition of indium also occurred in the liver and spleen if gelatin was included in the injection.[44]

Indium-iron-ascorbic acid complex, pH 9.0, remains in the blood for at least two hours after intravenous injection in man. During this period, as much as 81 per cent of the activity occurred in the blood, while only 0.9 per cent of the injected dose was excreted in the urine.[43] The disappearance of indium-113M EDTA injected into the iliac bone marrow of the rabbit provides an appropriate estimation of bone marrow blood flow. Drug-induced vasodilation decreased the biological half-life of indium in the marrow; vasoconstriction had the opposite effect.[45] Indium-113M glutathione injected into the rabbit remained mostly in the blood. The half-life of this compound was three times that of indium-EDTA.[46]

Indium-113M diethylenetriaminepentacetic acid (DTPA) accumulates in the brain, providing a useful brain scanning agent when indium DTPA is injected intravenously. In 87 patients, detection and characterization of intracranial lesions was satisfactorily accomplished with indium DTPA.[47] Oral administration of indium DTPA has been useful for the study of gastric emptying.[48] In rats with Yoshida sarcomas, the tumor to brain ratio of indium DTPA was 34:1.[27] Excretion occurs via the kidney[49,50], making indium-DTPA useful for kidney scanning. An indium-iron DTPA-ascorbic acid complex was useful in distinguishing between renal cysts and neoplasms.[51]

Eighty-two per cent of indium-113M sulfur colloid was found in the liver and bone marrow, illustrating the specific accumulation by the reticuloendothelial system. Indium chondroitin sulfate colloid is also accumulated by the reticuloendothelial system, specifically the bone marrow.[52]

B. Absorption and Excretion

Intestinal absorption of orally administered indium compounds is apparently not great. The LD_{50} for oral administration of indium sulfate is, for example, almost 200 times the LD_{50} for intravenous administration. The oral LD_{50} for indium oxide in mice is about 10g per kg, compared with the intravenous LD_{50} of about 0.5 mg per kg. Most of the orally administered indium is excreted in the feces.

The mode of injection, as well as the particular compound involved, influences the mode of excretion. For example, intravenously injected indium chloride is mainly excreted in the urine; however, intraperitoneally injected indium chloride is mainly excreted in the feces, being accumulated by the liver and passed into the small intestine in the bile. Indium chelates are excreted principally by the kidney, but the fecal excretion of high doses of indium sulfate injected intravenously into mice was seven to eight times the amount excreted in the urine.[53]

It appears that the indium compounds which are most readily accumulated by the liver are most likely to appear in the feces, whereas compounds which remain in the vascular system are predominantly excreted by the kidneys.

C. Metabolic Effects and Biochemistry

Indium (±3) inhibited the enzyme-catalyzed conversion of isocitrate to alpha ketoglutarate in the presence of NADPH.[54] Four injections of seven mg of indium sulfate into rats markedly influenced the urea cycle. The transfer of glutamic acid to ornithine was blocked, while glutamic acid was transformed to proline.[55] Trivalent metal cations inhibit ferrooxidase (ceruloplasmin EC 1. 12. 3.1). The metal ions studied in order of decreasing effectiveness of inhibition were: indium>zirconium oxide>aluminum>scandium>gallium.[56] Indium is thought to influence a metalloenzyme necessary for limb bud development in hamster embryos of mothers injected intravenously with indium.[57]

Subcutaneous injection of indium compounds produces local tissue calcification. This response is prevented by the systemic administration of an iron-dextran preparation.(58)

Indium sulfate added to the liquid culture medium enhanced the rate of nitrification of Nitrobacter agilis up to an optimum concentration.(59)

Pretreatment of plasma proteins with EDTA affects the *in vitro* binding of indium-113M. The results of the experiments suggest that indium binding to serum protein occurs in two stages: the first is through a multivalent anion, which is released during saturation binding.(60)

Studies comparing the *in vitro* deposition of transferrin-bound indium-111 (+3) and iron-59 (+3) demonstrated that the characteristics of their transport into reticulocytes were very similar, if not identical.(38)

The interaction of indium (±3) with a phospholipid monolayer was studied at various concentrations of indium. Indium decreased the surface pressure of the monolayer, suggesting that indium and other heavy metal ions may disrupt biomembranes to some extent.(61)

D. Pharmacology

The biological halflife of indium-114M injected into rabbits was 6.8 days The highest concentration was found in the kidneys, the lowest in the heart. Histological examination of different organs revealed extensive damage, especially to the kidneys and liver.(62) Blood clotting was studied in 79 patients before and after administration of radioindium compounds. The change in blood clotting factors and coagulation process depended on the target organ of the indium compound used. Although the blood clotting changes were significant, no clinical manifestations were observed since the deficits in clotting factors were only partial and compensated each other.(63)

Dogs were injected with 200 ml. of indium-iron hydroxide pellets (138,000 particles per ml) in the main pulmonary artery. After 100 ml. of particles, a significant increase occurred in the blood pressure in the pulmonary artery. However no changes occurred in the pulmonary diffusion capacity or venous oxygen capacity.(64)

Calcium deposits occurred at the site of subcutaneous injection of indium chloride (0.2 mg) six days after injection in young, but not in adult, rats.[65]

IX. ENVIRONMENTAL EFFECTS: BIOACCUMULATION

The transport of radioactive indium through the food chain poses a possible hazard to man. Bioaccumulation of indium-114M by the Atlantic croaker, Micropogon undulatus, was studied. The biological half life of indium in this food fish was 224 days. The radioactivity half life of indium-114M is 40.2 days. The conclusion drawn was that fish retaining large amounts of indium-114M could pose a hazard to public health.[66]

X. TOXICITY

A. Humans

1. Occupational Exposures

Individuals exposed to indium compounds during the production of indium complained of tooth decay, pains in joints and bones, nervous and gastrointestinal disorders, heart pains, and general debility.(67)

2. Other Exposures

Out of 770 patients injected with indium-113M radiopharmaceuticals for liver scanning, three developed anaphylactoid reactions. These three patients had cancer and an altered general condition. Vascular shock set in immediately or within 20 minutes after intravenous injection and lasted from 10 minutes to an hour.

In a parallel study of coagulation in patients receiving labelled or unlabelled indium compounds, changes in intravascular coagulation were observed. During the first two hours after injection, hypercoagulation with increased platelet adhesiveness occurred. After twenty-four hours, and five days later, lengthened coagulation time were observed with decreases in platelet adhesiveness and fibrinogen concentration.(68)

The toxic effects of indium can be reduced by the use of carrier-free radioactive isotopes.

B. Mammals

1. Acute and Subacute Toxicity

In mice, hydrated indium oxide injected intravenously is forty times more toxic than ionic indium on a weight basis. The LD_{50} for hydrated indium oxide was 0.323 ± 0.063 mg per kg body weight. For ionic indium, the LD_{50} was 12.5 ± 0.6 mg per kg. Lethal amounts of ionic indium produced inactivity of the animals and hind leg paralysis one day after injection; rapid and spasmodic respiration, weight loss and abnormal pelt after two days; at three days the mice became totally inactive and died by day four. In addition to the above symptoms, lethal doses of hydrated indium oxide produced muscle tremors and clonic convulsions after two to three days; the mice bled from the mouth, nose, ears, and intestines before they died on day three.(28)

Ionic indium is nephrotoxic, causing damage in the proximal convoluted tubule. At high doses, focal necrosis in the liver occurs. Extensive hemorrhaging and marked thrombocytopenia were caused by hydrated indium oxide. Fibrin thrombi were observed in the liver.[28]

The concentration of insoluble indium compounds resulting from phagocytosis by the reticuloendothelial cells may represent the mechanism for the progressive toxic effects.[28] For example, colloidal indium hydroxide was forty times as toxic as ionic indium in mice.[28] Blocking of the reticuloendothelial system resulted in decreased toxicity of indium hydroxide.[33]

The severe necrosis and fatal icterus produced by indium chloride injection into rats could be prevented by injection of ferric dextrans.[69] The LD_{50} after seven days for a single intraperitoneal injection of indium chloride to the albino rat was 1.8 mg per kg; the intravenous eight day LD_{50} was 4.1 mg per kg. The principle site of injury following intraperitoneal injection was the liver. The proximal convoluted tubule of the kidney was the principal site of injury with intravenous injection. An increase in neutrophil count and decrease in lymphocytes occurred in rats injected intravenously with indium chloride over a four month period.

The LD_{50}'s for the rat for indium sulfate, expressed in mg-atoms indium per kg body weight are: 20.5 for oral dose, 2.76 for intraperitoneal injection, and 0.11 for intravenous. Massive congestion of all organs, particularly the liver and kidneys, peaked at about four days after injection. Survivors show complete recovery 30 to 90 days after exposure.[53]

Intraperitoneal injection of indium nitrate to mice has an LD_{50} of 0.1 g per kg. The LD_{100} was 0.5 g per kg. The LD_{50} for indium nitrite was 4.2 g per kg with intragastric administration. The oral administration of indium oxide to mice had an LD_{50} of about 10 g per kg.

The LD_{50} of indium antimonide following oral administration was 3.7 g per kg. The greatest toxicity occurred after intratracheal administration, with alterations in the pulmonary tissue and dystrophic changes in parenchymatous tissue.[70]

The intratracheal administration of a dust containing 0.1 per cent indium in 25 and 50 mg doses resulted in 100 per cent lethality in guinea pigs.(71)

2. Chronic Toxicity

Rabbits given 0.16 g indium nitrate per kg daily for 4.5 months had decreased serum albumin and increased alpha-2-and gamma-globulins.(72) Aqueous indium sulfate (0.1 to 1.0 mg indium per kg per day) injected into mice for 15 days produced marked anemia and damage to the lungs, liver and spleen. Pulmonary lesions were quite evident.(73) In male rats killed 2 to 49 days after subcutaneous injection of indium triacetate (80 mg per kg), adrenal hypertrophy at the expense of both the cortical and medullary layers was observed, and enlarged nuclei were seen in the cells.(74)

Topical application of 0.1 per cent indium nitrate to intact tooth enamel at pH 1.7 to 3.2 produced partial dissolution. This finding supports the clinical evidence that topical indium nitrate increases caries incidence.(75)

The physicochemical properties of metal cations could be related to their acute doses on rabbit, rat and mouse. The log of the lethal dose of metal ions decreases linearly with the increase in the log of the stability constant of the metal EDTA complex, which is the product of the electro negativity and the ionic charge.(76)

3. Teratology

Indium nitrate injected into the hamster on the eighth day of gestation caused a high incidence of malformation of the digits of the offspring, including fusion, stunting and polydactyly. Doses above one mg per kg were completely embryopathic.(57)

C. Plants

Indium was toxic to cucumber seedlings, producing disorientation of the roots.(77)

D. Microorganisms

Indium (+3) is toxic to Chlorella vulgaris.[78] In Azotobacter strains, indium (+3) had an intermediate effect on growth, pigmentation and slime formation.[79]

E. Results of Personal Contacts with Medical Personnel

A total of 74 toxicologists and medical examiners throughout the United States were contacted by telephone or letter with regard to their professional acquaintance with incidences of accidental poisoning by indium or indium compounds. Of the 31 responses received, none reported any such instances.

XI. CURRENT REGULATIONS

No specific regulations for shipment of indium or its compound were found. In view of the recommended "threshold limiting value" assigned to this group, they must be treated as class B poisons. This requires a "Poison" label on all containers for shipments.

XII. STANDARDS

The Threshold Limit Value for indium and its compounds is 0.1 mg/m^3. This value is recommended in view of the character and severity of injury from indium salts, especially the pulmonary effects. Indium and its compounds may decompose to form the hazardous product indium sesquioxide.[2]

XIII. SUMMARY AND CONCLUSIONS

A. Summary

Indium production figures for the United States are not available, but the domestic production is probably less than 20 metric tons per year. Imports provide the difference between production and requirements for indium. Both domestic and foreign sources of indium are as a byproduct from primary zinc recovery. A new application for indium, indium-plated connectors for both copper and aluminum cables, requires about three per cent of the indium used in the U.S. This is the only major change noted in indium usage and comes within the current primary uses (solders, alloys and semiconductor devices).

Another area in which indium is important is medical applications. Since compounds of various radionuclides of indium are organ-specific, radioactive compounds of indium are used in diagnostic organ scanning. Toxicity of radioactive indium compounds is slight, only 3 of 770 patients showing some effects.

Indium and its compounds are considered moderately toxic and as a local irritant on contact with the skin. However, they are rated extremely toxic on ingestion. The American Conference of Governmental Hygienists has recommended a Threshold Limiting Value of 0.1 mg/m^3 based almost entirely on experiments with animals and the severity of injury from indium salts. The data involving humans is very limited. As a result possibly too much weight is given to a Russian report that individuals exposed to indium compounds during production complained of pains in joints and bones, tooth decay, nervous and gastrointestinal disorders, heart pains and general debility. This has not been reported in comparable U.S. activities.

Indium is poorly absorbed through the intestine, and oral levels of toxicity are quite high. The cells of the reticuloendothelial system phagocytize indium compound particles, and indium toxicity is apparently due to the concentration of heavy metals by these cells. Radioisotopes of indium are used for diagnostic x-ray scanning. Carrier-free isotopes can be used with relatively few toxic effects, although several cases of anaphylactic shock have occurred following injection of indium compounds.

The distribution of indium in the body can be controlled by the chemical form of the indium, the suspension medium and the mode of injection. Some indium salts apparently exert antitumor activity, but the toxic side effects make treatment difficult.

Effects of indium on lower animals, plants, and microorganisms are little known.

B. Conclusions

The following conclusions are based on the information contained in this report:

(1) Little is known concerning the effects of indium and its compounds on lower animals, plants, and microorganisms.

(2) Even with a relative lack of knowledge concerning potential environmental effects of indium, the amount released to the environment is so small as to be insignificant.

(3) Although there appears to be potential for occupational hazards to personnel in industries producing or utilizing indium, significant detrimental effects have not been reported in this country.

C. Recommendations

No recommendations for further study on indium appear justifiable at this time.

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